REMARKS/ARGUMENTS

Applicants respectfully request consideration of the enclosed amendments in response to the Office Action of January 5, 2004. A properly executed Revocation of Power of Attorney and Appointment of New Power of Attorney is enclosed for entry in the file history.

Claims 10, 25, 27-30, 34, 37-39, and 41-48 are pending in this application. Applicants have canceled claim 35. Claims 28, 30 and 37 were previously presented. Applicants have amended claims 10 25, 27, 29, 34, 38, 39 and 41 and added claims 42-48. New claim 42 depends from claim 39; new claim 44 depends from new claim 42 and new independent claim 43, new claim 45 depends from new claim 43, and new claims 45-48 depend from amended claim 10. Support for the subject matter of the new claims and for the amendments to the existing claims is found throughout the specification.

35 U.S.C.§112, Para. 2

The Examiner rejected claims 10, 25, 27-30, 34-35, 37-39 and 41 under 35 U.S.C.§ 112, para. 2 as being indefinite because claim limitation "CYP3A4 enzyme" is ambiguous and confusing because it does not define the metes and bounds of the term.

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the application disclosure; (2) teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. MPEP 2173.02. In reviewing a claim for compliance with 35 U.S.C. §112, para 2,

the Examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and therefore serves the notice function required by the statute. Id. (citing e.g., *Solomon v. Kimberley-Clark Corp.*, 216 F.3d 1372, 1379 (Fed. Cir. 2000)). A functional limitation must be evaluated and considered for what it fairly conveys to a person of ordinary skill in the pertinent art. MPEP 2173.05(g); *Ex parte Wu*, 10 USPQ2d 2031, 2033 (BPA&I 1989) ("[I]n rejecting a claim under 35 U.S.C. §112, para 2, it is incumbent on the examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims.")

Applicants have amended claim 10 so that step (iii) is directed to "determining whether a test compound that selectively binds to the ligand binding domain of said polypeptide induces receptor binding to a response element in the CYP3A4 gene promoter and expression of a cytochrome P-450 3A4 monooxygenase enzyme." Applicants urge that a person of ordinary skill in the art, reading claim 10 as amended in light of the specification, would have been able to ascertain the metes and bounds of the claim. Applicants therefore request withdrawal of this rejection.

35 U.S.C. 102(e)

(1) Berkenstam reference

The Examiner alleged that Applicants' arguments filed Sept. 5, 2003 have been fully considered but they are not found persuasive. These arguments were

directed to overcoming the rejection expressed in the Office Action of June 16, 2003 under 35 U.S.C.§ 102(e) as being anticipated by Patent Application Publication No. US 2003/0032790 to Berkenstam et al. The Examiner applied the pre-AIPA form of 35 U.S.C.§ 102(e).

Applicants respectfully request that the Examiner expressly indicate whether he has withdrawn this rejection of the pending claims. If the Examiner has not withdrawn this rejection, Applicants respectfully request that the Examiner state his reasons. MPEP 201.15 provides that "[w]hen the necessary papers are filed to overcome the date of the reference, the examiner's action, if he or she determines that the Applicants are not entitled to the priority date, is to repeat the rejection on the reference, stating the reasons why the Applicants are not considered entitled to the date. If it is determined that the Applicants are entitled to the date, the rejection is withdrawn in view of the priority date."

Pre-AIPA 35 U.S.C. §102(e) provides that an applicant is entitled to a patent unless the claimed invention was described in a United States patent to another having an effective United States filing date before applicant's date of invention. 35 U.S.C. § 102(e). The effective U.S. filing date of a reference includes the benefit of domestic priority.

U.S. Application 09/143,828, entitled "Novel Vitamin D Receptor Related Polypeptides, Nucleic acid Sequence Encoding the Same and Uses Thereof," was filed Aug. 31, 1998 by Berkenstam and Dahlberg and published Feb. 13, 2003 as U.S.2003/0032790 A1. It claims foreign priority to Swedish Patent 9801148-9, filed Mar. 31, 1998, and Swedish Patent 9703745-1 (filed Oct. 14,

1997). Domestic priority is based on U.S. provisional application No. 60/067,373 (filed Dec. 3, 1997).

In order to qualify as a prior art reference under 35 U.S.C. §102(e), a parent application must support the invention claimed as required by 35 U.S.C. §112, para. 1. MPEP 2136.03 (IV). Applicants urge that the present invention was not described in a cited reference prior to invention by the Applicants and therefore is not anticipated under 35 U.S.C.§ 102(e). Applicants respectfully refer the Examiner to the attached copies of Swedish Patent 9801148-9 (Exhibit 1), Swedish Patent 9703745-1 (Exhibit 2) and U.S. provisional application No. 60/067,373 (Exhibit 3).

Applicants urge that Figure 8 of the 2003 Berkenstam publication, which shows the deduced amino acid sequence of VDRRg-2, is not found in the 1997 priority documents. The VDRRg-2 disclosure on page 4, para. 61-78 of the Berkenstam publication also does not appear in any of the priority documents. Therefore the earliest effective filing date to which Berkenstam is entitled for this subject matter is Aug. 31, 1998, i.e., after the priority date of the present application, which is a continuation-in-part of the '935 application, filed March 26, 1999, which claims priority from Provisional Application 60/079,593, filed March 27, 1998.

Since Berkenstam is not prior art, Applicants respectfully request that the Examiner withdraw this rejection, if he has not already done so.

(2) **Evans reference**

The Examiner rejected claims 10, 25, 27-30, 34-35, 37-39 and 41 under 35 U.S.C. §102(e) as being anticipated by Evans et al. (US2003/0064430 A1). The Examiner alleged that Evans (1) teaches the method of identifying a ligand to the polypeptide SXR (page 6, para. 73); (2) discloses SXR polypeptide (SEQ ID NO: 2), which is 100% identical to the claimed SEQ ID NO: 14 domain (page 3); and (3) discloses cytochrome P450 expression and CYP3A expression as activated by various activators (page 2, column 9). The Examiner further alleged that the name of the enzyme ("CYP3A4") does not distinguish over the art because no structural differentiation is claimed.

"Anticipation is a question of fact and is determined by first construing the patent claims and then comparing the properly construed claims to the prior art." *In re Cruciferous Sprout Litig.* 301 F.3d 1343, 1346 (Fed. Cir. 2002). Anticipation requires that each and every element of the claims be disclosed, either expressly or inherently, in a single prior art reference or embodied in a single prior art device or practice. *See In re Paulsen*, 30 F.3d 1475, 1478 (Fed. Cir. 1994); *Minnesota Min. & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565 (Fed. Cir. 1992). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of invention. *See Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). A finding of anticipation "is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations." *Id.* Absence of any claim element from the reference

negates anticipation. *See Kloster Speedsteel AB v. Crucible, Inc.*, 793 F.2d 1565, 1571 (Fed. Cir. 1986).

An anticipatory reference must also enable a skilled artisan to make and use the claimed invention. *See Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1374, 58 U.S.P.Q.2d 1508 (Fed. Cir. 2001)(*citing In re Donohue*, 766 F.2d 531, 533, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985)). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993).

A rejection based on 35 U.S.C. §102(e) can be overcome by persuasively arguing that the claims are patentably distinguishable from the prior art, and by amending the claims to patentably distinguish over the prior art. MPEP 706.02(b).

For the following reasons, Applicants urge that the present invention was not described in the Evans reference and therefore is not anticipated under 35 U.S.C. §102(e).

(1) <u>The Method of Claim 10</u>

The Examiner alleged that Evans (1) teaches the method of identifying a ligand to the polypeptide SXR (page 6, para. 73). To expedite prosecution, Applicants have amended claim 10 to require that a test compound <u>selectively</u> bind to a polypeptide comprised of a ligand binding domain of human pregnane X receptor (hPXR) having the amino acid sequence 141-434 of SEQ ID NO: 14. As disclosed in the specification on page 15, compounds that bind PXR with a

pKi > 5 can be screened for selectivity for PXR versus other nuclear receptors using standard binding assays. The specification further discloses that a compound that binds selectively to PXR has at least a 10 fold greater affinity for PXR, preferably at least a 100 fold greater affinity than, for example, the glucocorticoid receptor. Therefore compounds that bind PXR according to the present invention can be screened for selectivity for PXR versus other nuclear receptors using standard binding assays.

Applicants urge that Evans does not anticipate amended claim 10 which recites a method of screening a test compound for its ability to induce cytochrome P-450 3A4 (CYP3A4) gene expression comprising: (i) contacting said test compound with a protein comprised of a ligand binding domain of human pregnane X receptor (hPXR) having the amino acid sequence 141-434 of SEQ ID NO: 14, wherein the protein shares at least 96% amino acid sequence identity with the ligand binding domain of SEQ ID NO: 14 and retains the sequence's ligand-binding function; (ii) determining whether said test compound selectively binds to the ligand binding domain of said protein and (iii) determining whether a test compound that selectively binds to the ligand binding domain of said protein induces receptor binding to a response element in the CYP3A4 gene promoter and expression of a cytochrome P-450 3A4 monooxygenase enzyme as claimed in amended claim 10 herein. Indeed, a person of ordinary skill in the art would not be able to use the Evans method to distinguish binding of a ligand to hPXR from binding to other nuclear receptors without undue experimentation because Evans does not teach how to do so.

(2) The Sequence Element

The Examiner alleged that (2) Evans discloses SXR polypeptide (SEQ ID NO: 2), which is 100% identical to the claimed SEQ ID NO: 14 domain (page 3). Applicants respectfully disagree.

Based on a comparison of the Evans disclosure and the specification of the pending application, a person of ordinary skill in the art would understand that SEQ ID NO: 2 for SXR is different from SEQ ID NO: 14 for hPXR and that SXR is different from PXR.

First, the tissue distribution of Evans' SXR receptor is not identical to that of hPXR. Evans discloses that SXR mRNA is expressed substantially exclusively in the liver and intestine, and that longer exposures did not reveal expression in any other tissues (page 3, para 41). In contrast, Example 1 of the present invention discloses that both hPXR and mPXR are most abundantly expressed in the liver and tissues of the GI tract, including the colon and small intestine (Specification, page 25).

Second, the sequence of Evans' SXR receptor is different from the sequence of hPXR. Evans discloses that the preferred polypeptide of the SXR polypeptide has substantially the same amino acid sequence as shown in SEQ ID NO: 2 (Evans, page 3, para. 37), where "substantially the same" means sequences which typically share more than 95% identity (Evans, page 5, para. 57). Evans SEQ ID NO: 2 is composed of 464 amino acids, while SEQ ID NO: 14 of the present invention is composed of 434 amino acids. Even if a skilled artisan were to align Evans SEQ NO: 2 so that amino acid 30 is aligned with

amino acid 1 of SEQ ID NO: 14, Applicants urge that these sequences are neither identical nor substantially the same. Residue 217 in Evans SEQ ID NO: 2 is Pro, while residue 187 in the present invention is Ser; and residues 245, 246, 248-256, 259-263 of SEQ ID NO: 2 have a different sequence from residues 215, 216, 218-226, 229-233 in SEQ ID NO: 14 of the present invention:

Evans' SEQ ID NO: 2:

245 250 255 260

-Ala Ala Gly Gly Gly Trp Gln Cys Leu Glu Leu Gln Xaa Pro Ser Arg Gln Trp Arg-

Present invention SEQ ID NO: 14:

215 220 225 230

-Leu Arg Gly Glu Asp Gly Ser Val Trp Asn Tyr Lys Pro Pro Ala Asp Ser Gly Gly-

These sequence differences do not reflect conservative amino acid variations, such as substitution of a nonpolar residue for another nonpolar residue or a charted residue for a similarly charged residue as defined by Evans (page 3, para. 37), and are likely to substantially alter the tertiary structure of the protein. Therefore a person of ordinary skill would understand that 5% of the 434 amino acid sequence comprising the ligand binding domain of the present invention, i.e., amino acids 141-434 of the Fig. 1 sequence, is different from the prior art.

To expedite prosecution, Applicants have amended claims 10, 27 and 29 to reflect that the protein comprised of a ligand binding domain of hPXR having the amino acid sequence 141-434 of SEQ ID NO: 14 shares at least 96%, 97%

and 98%, respectively, amino acid sequence identity with the ligand binding domain of SEQ ID NO: 14 and retains the sequence's ligand-binding function.

(3) The Enzyme Expression Element

The Examiner alleged that Evans (page 2, column 9) discloses cytochrome P450 expression and CYP3A expression as claimed in the present application. Applicants respectfully disagree. The Examiner further alleged that the name of the enzyme in claim 10, "CYP3A4", does not distinguish over the art because no structural differentiation is provided.

To expedite prosecution, Applicants have amended claim 10 to reflect that the claimed method of screening a test compound for its ability to induce cytochrome P-450 3A4 (CYP3A4) gene expression comprises the expression of a cytochrome P-450 3A4 monooxygenase enzyme following receptor binding to a response element in the CYP3A4 gene promoter.

Fig. 3B of the present application shows the oligonucleotides used in band shift assays and the positions of nuclear receptor half-site motifs and mutations. Example 2 of the present invention further discloses that hPXR binds efficiently to the CYP3A4 IR6 PXR response element ("PXRE") as a heterodimer with RXR (Specification, pages 26-28). The Specification at page 26 further discloses that an IR6 motif contains two copies of the nuclear receptor half-site sequence AG(G/T)TCA organized as an inverted repeat (IR) and separated by 6 base pairs. The Specification further discloses that this half-site configuration is very different from that found in the CYP3A1 PXRE, which contains two half-sites

organized as a direct repeat (DR) with a three nucleotide spacer, defined as a DR3 motif (Specification, page 27).

The present invention also discloses that hPXR is activated by a diverse group of synthetic compounds known to induce CYP3A4 gene expression. Example 3 and Fig. 4 disclose that hPXR is activated by synthetic steroids (dexamethasone, dexamethasone-t-butylacetate, PCN, RU486, spronolactone and cyproterone-acetate), the antibiotic rifampicin, the antimycotic clotrimazole, the antihypercholesterolemic drug lovastatin, phenobarbital and the organochlorine pesticide transnonachlor, all of which are known to induce CYP3A4. Pregnenolone, progesterone and 5-β-pregnane-3,20-dione, naturally occurring steroids previously shown to activate mouse PXR1, all activated hPXR roughly four-fold, while the 17-hydroxy derivatives of pregnenolone and progesterone were weak activators. The Specification further teaches that these natural steroids are unlikely to be natural hPXR ligands (pages 29-30).

Based on Evans' disclosure, a skilled artisan would have no reason to believe that his SXR receptor has the same binding characteristics as does the hPXR receptor of the present invention. Evans does not disclose that his SXR receptor binds to CYP3A4 response elements. Instead, Evans discloses that CYP2A1, CYP2A2, CYP2C1, CYP2C6, CYP3A1, CYP3A1, CYP3A2, P450 oxidoreductase and UDP-glucuronosyltransferase genes contain putative SXR response elements (Evans, page 4, para. 47). Furthermore, Evans does not disclose that SXR is activated by anything other than by natural and synthetic steroids and their metabolites (Evans, page 4, para. 48, p. 5, para. 53, and Fig.

4). In addition, Evans does not disclose that SXR can activate IR6 elements, but only that SXR can activate DR3, DR4 and DR5 elements in genes for a number of steroid hydrolases (Evans, page 4, para. 48 and Fig. 4). Evans further discloses that SXR:RXR heterodimers showed strong binding selective to a DR-4 motif, with minimal binding to DR-3 and DR-5 motifs, and substantially no binding to other spacing motifs. Evans further discloses that when the related half-site AGTTCA (βDR) was used, strong binding was seen on both β-DR-4 and β-DR5 motifs, and significant, but reduced binding to the β-DR-3 motifs (Evans pages 3-4, para. 42).

Since there is no prior art which teaches or suggests the claimed invention, Applicants respectfully request that the Examiner withdraw all objections to and rejections of the present invention.

Applicants urge that this application is now in condition for allowance and earnestly solicit early and favorable action by the Examiner. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is respectfully urged to telephone the undersigned at 212-801-2116. The undersigned may also be contacted via e-mail at lubitb@gtlaw.com.

AUTHORIZATION

The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 50-1561.

Respectfully Submitted,

By:

Date: July 6, 2004

BEVERLY W. LUBIT
Attorney for Applicants
Registration No. 47,759

Greenberg Traurig, LLP
885 Third Avenue, 22nd Floor
New York, NY 10022-4834
(212) 801-2100

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